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EXAMINER	
BERTAGNA, ANGELA MARIE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,628	ADRA, CHAKER N.	
	Examiner	Art Unit	
	Angela M. Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 49* is/are pending in the application.

4a) Of the above claim(s) *7,8 and 17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9-16 and 49* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. 1. Applicant's election of Group I, claims 5, 6, 15, and 16, in the reply filed on May 18, 2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Linking claims 1-4, 9-14, and 49 will also be examined with the elected claims.

Claims 7, 8, and 17-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 18, 2010.

Application Data Sheet

2. Applicant's submission of an Application Data Sheet on September 5, 2006 is acknowledged. It is noted that the citizenship of Inventor Adra is not consistent between the oath and the Application Data Sheet. MPEP 601.05 provides the following guidance regarding this situation:

> Pursuant to 37 CFR 1.76(d)(3), the oath or declaration under 37 CFR 1.63 or 37 CFR 1.67 governs inconsistencies with the application data sheet in the naming of inventors and setting forth their citizenship. If different inventors are listed in the application data sheet than are named in the oath or declaration for the application, the inventors named in the oath or declaration are considered to be the inventors named in the patent application. See 37 CFR 1.76(d)(3). Any change in the inventorship set forth in the oath or declaration under 37 CFR 1.63 must be by way of a request under 37 CFR 1.48(a) notwithstanding identification of the correct inventive entity in an application data sheet or supplemental application data sheet. Similarly, if the oath or declaration under 37 CFR1.63 incorrectly sets forth the citizenship of one of the inventors, that inventor must submit a supplemental oath or declaration under 37 CFR 1.67 with the correct

citizenship notwithstanding the correct identification of the citizenship in an application data sheet or supplemental application data sheet.

Drawings

3. The drawings filed on September 5, 2006 are acceptable.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see pages 18, 21, and 27). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

5. Claim 13 is objected to because of the following informalities: A hyphen should be inserted between the words "granulocyte" and "selective" in line 2.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph (Scope of Enablement)

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 9-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting statistically significant differences in the mRNA expression pattern observed between normal, healthy mammalian subjects and

mammalian subjects known to possess a granulocyte disorder, does not reasonably provide enablement for diagnosing any granulocyte disorder in any biological sample obtained from any subject based solely on the mRNA expression level of a single granulocyte-selective marker. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The nature of the invention

The methods of the instant claims are classified in the unpredictable arts of biochemistry and molecular biology and are drawn to methods for diagnosing a granulocyte disorder based on differential expression of granulocyte-selective markers.

The breadth of the claims

The methods of the instant claims are extremely broad in scope. Claims 1-6 and 9-13 encompass diagnosing any granulocyte disorder (*e.g.*, asthma, atopic dermatitis, eosinophil-associated leukemias, basophil-associated leukemias, Cushing's syndrome, eosinophilic gastrointestinal disorders, eosinophilic pneumonia, and neutrophil disorders) in any mammalian

subject (*e.g.*, humans, dogs, cats, horses, goats, cows, mice, or rats of known or unknown disease status) by observing differential expression of a single granulocyte-selective marker in any biological sample obtained from the subject. Claim 14 is also very broad in scope, encompassing diagnosing any non-neutrophil or mast cell disorder in any mammalian subject by observing differential expression of a single granulocyte-selective marker in any biological sample obtained from the subject. Claims 15 and 16 limit the disorder to a basophil disorder and a basophil-associated cancer or tumor, respectively.

Guidance in the Specification and Working Examples

The specification generically teaches that detection of at least one differentially expressed granulocyte-selective transcript can be used to diagnose granulocyte disorders, such as asthma, (pages 2-4 and pages 12-14). The working examples describe experiments in which granulocyte-selective transcripts were identified by subjecting purified cells obtained from normal, healthy human subjects to microarray analysis and comparing the results for different blood cell types (pages 17-27). Real-time RT-PCR was used to verify the microarray results for four of the identified transcripts (page 19). However, the working examples do not describe diagnosing an individual of unknown disease status with respect to even one of the many granuloyte disorders encompassed by the claims based on the observed expression level of any one or more of the disclosed granulocyte-selective markers. The specification and working examples also do not contain any discussion of methods for validating such diagnostic methods.

State of the Prior Art and Unpredictability in the Art

As discussed in greater detail below, the prior art of Yawalker et al. (Journal of Investigative Dermatology (1999) 113: 43-48), Csiszar et al. (Clinical and Experimental Immunology (2000) 122: 464-470), and Nowicki et al. (Oncogene (June 2003) 22: 3952-3963) teach methods falling within the scope of the claimed genus of methods. The prior art does not teach diagnosing a granulocyte disorder in mammalian subjects of unknown disease status based solely on the mRNA expression level of one or more granulocyte-selective markers, however.

The teachings of Erle et al. (Genome Biology (2003) 4: 232) are indicative of the state of the art at the time of the invention and the level of unpredictability in the art. Erle teaches that microarrays and/or quantitative RT-PCR could be used to identify differences in gene expression patterns between normal subjects and subjects known to be afflicted with a granulocyte disorder, such as asthma (see pages 1-2). However, Erle cautions that asthma is a very complicated disorder and that further validation of the results obtained from microarray analysis of mRNA expression patterns is required before observed gene expression differences between a normal and asthmatic subject can be used in a stand-alone method of diagnosing subjects of unknown disease status (see pages 2-3). Erle also teaches that this process is likely to be "challenging", due to the complexity of the disease, the need to obtain results from a large number of individuals in a well designed cohort, and "the difficulties inherent in obtaining suitable tissue for study" (see page 3). Similarly, Nowicki teaches that further validation of the observed chronic myelogenous leukemia mRNA expression signature is needed before the results can be used in a stand-alone assay for diagnosing human subjects of unknown disease status, since the disease is complex and there are differences in the cell composition of the normal and leukemia

samples used in the study (page 3961). Thus, based on the teachings of Erle and Nowicki, the methods of diagnosing a granulocyte disorder in human subjects of unknown disease status based solely on differential gene expression results encompassed by the claims are not well-developed and are associated with a high degree of unpredictability. Given the complexity of granulocyte disorders in general and the challenges inherent in extending results obtained in one species of subject to another species, the full scope of the claimed methods is associated with a high degree of unpredictability.

Quantity of Experimentation

The quantity of experimentation in this area is immense, since, as discussed above, there is a very high degree of unpredictability as to whether the mRNA expression level of one or more of the disclosed granulocyte-selective markers can be used to reliably and reproducibly diagnose human or other mammalian subjects of unknown disease status as having one or more of the granulocyte disorders encompassed by the claims. For each of the different granulocyte disorders and each different type of subject encompassed by the claims, the ordinary artisan would have to determine an appropriate sample for analysis, identify a combination of one or more granulocyte-selective markers displaying statistically significant changes in mRNA expression levels between normal and diseased individuals, and determine that the expression level changes can be used to reliably diagnose subjects of unknown disease status. The results for each different subject and granulocyte disorder would not necessarily extend to other subjects and disorders given the differences between them. Furthermore, this large quantity of unpredictable experimentation would have to be undertaken with minimal guidance from the

prior art and the specification and with no guarantee of success. Accordingly, the amount of experimentation required for the ordinary artisan to practice the full scope of the claimed methods is considered to constitute an undue amount of experimentation.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the claimed methods are broadly drawn to a method for diagnosing any granulocyte disorder in any mammalian subject based solely on an observation of differential mRNA expression of at least one granulocyte-selective marker in a biological sample obtained from the subject. As discussed above, the claimed methods are associated with a high degree of unpredictability. Despite the breadth of the claims and their inherent unpredictability, the specification provides only minimal guidance regarding practice of the full scope of the claimed methods and provides no evidence to establish that detecting a statistically significant difference in the mRNA expression level of a granulocyte-selective marker is sufficient for diagnosis of a granulocyte disorder in a mammalian subject. As noted above, these aspects of the claimed methods are also not described in the prior art. Finally, the quantity of experimentation required to practice the full scope of the claimed methods is very large. Thus, given the broad claims in an unpredictable art, the large quantity of unpredictable experimentation required to practice the full scope of the claimed methods, the minimal guidance provided in the specification, the limitations of the working examples, and the negative teachings

in the art, balanced only against the high skill level in the art, the inevitable conclusion is that it would require undue experimentation for one of skill in the art to successfully practice the full scope claimed methods.

Claim Rejections - 35 USC § 112, 2nd paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 9-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 and 9-16 are indefinite, because the relationship between the reference level of expression and the expected level of expression recited in independent claims 1 and 14 is unclear. Claims 1 and 14 recite a step of comparing an observed expression level of at least one granulocyte-selective marker with a reference expression level and go on to discuss the observed expression level relative to an expected level of expression for the at least one granulocyte-selective marker. It is not clear from the claim language whether the reference level of expression and expected level of expression are intended to refer to the same or different values. If the former was intended, amending the claim to use consistent terminology throughout is suggested. If the latter was intended, amending the claim to further describe the relationship between the expected and reference expression levels is suggested.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 2, 4-6, 9, 11, and 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Yawalker et al. (Journal of Investigative Dermatology (1999) 113: 43-48).

These claims are drawn to a method for diagnosing a granulocyte disorder based on the expression level of one or granulocyte-selective markers.

Regarding claims 1, 2, 4-6, 9, and 13-15, Yawalker teaches a method for diagnosing a granulocyte disorder, specifically atopic dermatitis, which is a basophil disorder, that comprises using RT-PCR to measure the mRNA expression level of CCR3, which, as evidenced by Figure 3 of the instant application, is a granulocyte-selective marker, in a tissue sample obtained from a subject and comparing the observed CCR3 mRNA expression level to a reference CCR3 expression level, specifically the CCR3 mRNA expression level in a normal subject (see abstract, pages 43-46, and Figures 4-5). Yawalker further teaches that the mRNA expression level of CCR3 in the atopic dermatitis subjects is higher to a statistically significant degree compared to normal subjects, and, therefore, indicative of atopic dermatitis in the subject (see pages 45-46). Finally, it is noted that the preambles of independent claims 1 and 14 have not been accorded patentable weight, because they only state an intended use of the disclosed

method and do not further limit the positively recited method steps, which are disclosed by Yawalker (see MPEP 2111.02).

Regarding claim 11, Yawalker teaches that an abnormally high number of eosinophils are present in the studied tissue samples (pages 46-47).

10. Claims 1-6, 10, 12, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Csiszar et al. (Clinical and Experimental Immunology (2000) 122: 464-470) as evidenced by Courtney et al. (Annals of the Rheumatic Diseases (1999) 58: 309-314).

These claims are drawn to a method for diagnosing a granulocyte disorder based on the expression level of one or granulocyte-selective markers.

Regarding claims 1-3, 5, 6, 10, and 13, Csiszar teaches a method for diagnosing a granulocyte disorder, specifically systemic lupus erythematosus (SLE), which, as evidenced by Courtney, is a granulocyte disorder, that comprises using RT-PCR to measure the mRNA expression level of IL-4 which, as evidenced the instant application at Figure 6A-1, is a granulocyte-selective marker, in a blood sample obtained from a subject and comparing the observed IL-4 mRNA expression level to a reference IL-4 mRNA expression level, specifically the IL-4 mRNA expression level in a normal subject (see abstract, pages 465-466, Figure 4, and Table 3). Csiszar further teaches that the mRNA expression level of IL-4 in the SLE subjects is lower to a statistically significant degree compared to normal subjects, and, therefore, indicative of SLE in the subject (see pages 466-469). Finally, it is noted that the preamble of independent claim 1 has not been accorded patentable weight, because it only states an intended use of the

disclosed method and does not further limit the positively recited method steps, which are disclosed by Csiszar (see MPEP 2111.02).

Regarding claim 4, the blood sample used in the method disclosed by Csiszar is also a tissue sample, since blood is a tissue.

Regarding claim 12, as evidenced by Courtney (see abstract and pages 312-313), SLE is associated with an abnormally low number of neutrophils in the blood.

11. Claims 1-5, 10, 11, and 13-16 are rejected under 35 U.S.C. 102(a) as being unpatentable over Nowicki et al. (Oncogene (June 2003) 22: 3952-3963).

These claims are drawn to a method for diagnosing a granulocyte disorder based on the expression level of one or granulocyte-selective markers.

Regarding claims 1-5, 10, 11, and 13-16, Nowicki teaches a method for diagnosing a granulocyte disorder, specifically chronic myelogenous leukemia, which is a basophil disorder characterized by abnormally high numbers of eosinophils and basophils, that comprises using array hybridization to measure the mRNA expression level of carbonic anhydrase IV, which, as evidenced by Figure 6A-1 of the instant application, is a granulocyte-selective marker, in a blood or bone marrow sample obtained from a subject and comparing the observed mRNA expression level to a reference mRNA expression level, specifically the mRNA expression level in a normal subject (see abstract, page 3953, column 2, page 3961, and Figure 3). Nowicki further teaches that the mRNA expression levels of in the chronic myelogenous leukemia subjects is higher to a statistically significant degree compared to normal subjects, and, therefore, indicative of chronic myelogenous leukemia in the subject (page 3953 and Figure 3). Finally, it is noted that the

preambles of independent claims 1 and 14 have not been accorded patentable weight, because they only state an intended use of the disclosed method and do not further limit the positively recited method steps, which are disclosed by Nowicki (see MPEP 2111.02).

12. Claim 49 is rejected under 35 U.S.C. 102(b) as being anticipated by Schroeder et al. (Clinical and Experimental Allergy (2001) 31: 1369-1377).

Claim 49 is drawn to a method for identifying a compound that alters at least one physiological property of a granulocyte.

Schroeder teaches a method for identifying a compound that alters at least one physiological property of a granulocyte comprising the following steps: (i) contacting a granulocyte, specifically a basophil, with a candidate compound (desloratadine) that interacts with a granulocyte-selective marker (see page 1370, column 2 – page 1375, column 1 and Figures 1-5; see also pages 1370 and 1376-1377, where the interaction between the candidate compound and granulocyte-selective markers is further discussed), (ii) determining at least one physiological property of the granulocyte after contact with candidate compound (pages 1371-1375 and Figures 1-5), and (iii) comparing the at least one physiological property of the granulocyte to at least one reference property to determine whether the candidate compound alters at least one physiological property of the granulocyte (pages 1371-1375 and Figures 1-5). Thus, the teachings of Schroeder anticipate the method of claim 49.

Conclusion

13. No claims are currently allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Yerramilli et al. (WO 99/10536 A1) teaches an array-based method for monitoring gene expression in granulocytes (see abstract).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela M. Bertagna whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Angela M Bertagna/
Examiner, Art Unit 1637